

Tuberculosis—Chemotherapy

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Standard chemotherapy with streptomycin, isoniazid, and para-aminosalicylic acid (PAS) administered according to the rules for optimal therapy will cure most patients with tuberculosis. The rules are deceptively simple and need to be applied with careful attention to detail since even minor deviations may result in failure and the emergence of drug resistance.

Standard Chemotherapy

Drug resistance is likely to occur when any antituberculosis drug is given alone. Hence two drugs to which the organisms are susceptible should be given. About 4% of previously untreated patients with pulmonary tuberculosis in Britain yield cultures resistant to one standard drug; resistance to two drugs is very rare.⁸ Initial therapy should therefore be triple, using isoniazid, streptomycin, and PAS, thus assuring that the patient receives at least two drugs to which the organisms are susceptible. Isoniazid, 300 mg, with sodium PAS, 12 g combined in a single medicament is given usually daily in two divided doses. Streptomycin, 1 g daily for patients under 40 years and 0.75 g daily in older patients, is given by injection. Triple therapy is continued for two or three months. Thereafter continuation therapy comprises two drugs, usually isoniazid and PAS, given for a total of 18 months or two years according to the severity of the disease.

As pointed out in the previous article, the role of initial drug resistance as a cause of failure of chemotherapy is very small compared with that of irregular administration of drugs. The policy of obtaining initial sensitivity tests routinely on all fresh cases of tuberculosis is of very little practical value, is disadvantageous to the patient where the tests are inaccurate, and in poor communities is a serious waste of financial and technical resources.

Alternative Companion Drugs to Isoniazid

Standard chemotherapy should be given wherever possible since it assures cure in almost every patient who takes the drugs as prescribed. Nine other antituberculosis drugs are available in Britain. The use of new and relatively untried drugs is to be deprecated. The major cause of poor results of chemotherapy is irregular self-medication. This problem is not overcome by the use of new drugs. Nevertheless, modification of standard chemotherapy may be necessary in certain special circumstances.

Streptomycin and PAS have two main disadvantages as companion drugs to isoniazid. Firstly, expense; in developing countries, where tuberculosis remains a common disease, streptomycin and PAS may be too expensive for mass chemotherapy. A cheap and effective companion drug to isoniazid is needed. Only thiacetazone is sufficiently cheap to fulfil this purpose. The second disadvantage comprises toxicity and allergy. About 15% of patients are unable to continue with PAS or streptomycin because of the gastrointestinal effects

of the former or ototoxicity of the latter drug. Allergy to these two drugs occurs in about 15% of patients. Desensitization is usually possible but an alternative drug may be required where the allergic reaction is severe or desensitization is inconvenient or troublesome.

Drugs which may replace PAS or streptomycin as companion drugs for isoniazid are thiacetazone, ethambutol, and rifampicin.

THIACETAZONE

The major advantage of thiacetazone is its cheapness. It is about one-tenth the cost of PAS and is almost as cheap as isoniazid. Thiacetazone, 150 mg, together with isoniazid, 300 mg, in a *single* daily oral dose was as effective as PAS and isoniazid in controlled studies in East Africa, India, and Hong Kong.⁴⁸ The dosage is critical, larger doses of thiacetazone being too toxic and lower doses being ineffective. Initial supplement with streptomycin, 1 g daily for the first two months of treatment, substantially improves effectiveness, attaining 90% bacteriological success in one study.⁴⁹ Increasing the dose of isoniazid does not improve efficacy.

Regarding toxicity, a co-operative study of the regimen in thirteen countries showed the incidence of adverse effects from thiacetazone to be in general similar to that of PAS, though in some races, particularly the Chinese, thiacetazone was more toxic.⁵⁰ Incorporation of vitamins and antihistamines in the medicament was unsuccessful in reducing thiacetazone toxicity.⁵¹

Pretreatment strains of tubercle bacilli in various parts of the world may vary in their degree of resistance to thiacetazone—for example, those from Southern India, Hong Kong, and Singapore, are more resistant than those from Britain and East Africa. These variations may affect response to treatment. Thus thiacetazone regimens in Singapore were shown to be less effective and also more toxic than similar regimens in India and East Africa.⁵²

Thiacetazone is cheap, of small bulk, keeps well in tropical conditions, and should be considered for use in economically undeveloped countries as an alternative to isoniazid alone. When contemplating the use of thiacetazone and isoniazid in a country for the first time a preliminary pilot study of toxicity and efficacy should be made, since results may differ from one country to another. Thiacetazone is also a useful alternative to PAS in patients unable to tolerate the latter drug because of gastrointestinal upset. It should not be used in patients who have been allergic to other antituberculosis drugs since allergic reactions to thiacetazone tend to be severe.

ETHAMBUTOL

Ethambutol is becoming popular as a companion drug to isoniazid because it is better tolerated than PAS. Controlled studies suggest that 25 mg/kg for the first two months followed by 15 mg/kg daily in a single dose is an acceptable replacement for PAS in initial treatment of pulmonary tuberculosis of minimal or moderate extent.⁵³ In advanced cavitated disease, however, it is probably not as effective as PAS.⁵⁴

Ethambutol may produce retrobulbar neuritis, characterized by blurring of vision, central scotoma or peripheral visual field constriction, and loss of ability to see green and red. Occasionally haemorrhagic retinopathy occurs. Prompt cessation of the drug

is usually followed by complete recovery, but continuation of the drug for long after the onset of symptoms may result in permanent impairment of vision and optic atrophy. Ocular toxicity is dose-dependent: it very rarely occurs at 15 mg/kg but at 25 mg/kg the incidence is about 15%, toxicity occurring usually after the first six months of therapy. Pretreatment ophthalmological examination before therapy is desirable and the patients should be warned to discontinue treatment immediately any visual disturbance is noted. Routine visual acuity estimations during treatment are of doubtful value.⁵⁵

Ethambutol is an acceptable replacement for streptomycin or PAS in patients unable to tolerate these drugs. Some doctors use ethambutol routinely instead of PAS as a companion drug to isoniazid, but it is probably not as effective as PAS in advanced disease, is more expensive, and when given in dosage greater than 15 mg/kg carries a risk of ocular toxicity.

RIFAMPICIN

Laboratory studies of rifampicin have shown it to have a greater bactericidal effect than that of any other antituberculosis drug. Rifampicin-isoniazid combinations in experimental tuberculosis sterilizes more rapidly than any previously tested drug combination, raising the hope that in man the duration of treatment could be shortened. Though rifampicin has been used with great enthusiasm by some doctors, the value of this drug in human tuberculosis remains unestablished and is the object of current evaluation, and the results are as yet preliminary.

Comparison of rifampicin-isoniazid with streptomycin-isoniazid over three months in an Italian study showed superiority of the rifampicin regimen.⁵⁶ An American study compared rifampicin-isoniazid and rifampicin-isoniazid-ethambutol with a control regimen of streptomycin-isoniazid-ethambutol. At four months bacteriological results of the rifampicin regimens were slightly superior to the control regimen.⁵⁷

Evidence about the hepatotoxicity of rifampicin in daily dose of 450-600 mg is highly conflicting. The Italian and American studies noted above found no important hepatotoxicity. In contrast, a French study of 50 tuberculous patients showed 12 cases of jaundice (four fatal), among whom five were alcoholics and three were receiving other potentially hepatotoxic drugs.⁵⁸ Rifampicin-induced jaundice has been observed in alcoholics.⁵⁹ Up to a third of patients receiving rifampicin may show rises in the serum transaminase levels during the first two months of therapy, which tend to become normal again during continuation treatment.⁶⁰ Liver enzyme disturbances appear to occur most frequently when rifampicin is combined with isoniazid, a drug which also provokes transient liver enzyme disturbances.⁶¹

Thrombocytopenia, purpura, and fever have been attributed to twice-weekly high-dosage rifampicin by several workers. Among 49 patients receiving 1,200 mg twice weekly thrombocytopenia was found in three and a febrile reaction with nausea and vomiting soon after taking rifampicin in eight. Antibodies to rifampicin were detected in 16.⁶² This unacceptably high incidence of adverse effects was not encountered in other studies using 900 mg twice-weekly.

Rifampicin is clearly a powerful antituberculosis drug but its efficacy compared with standard triple chemotherapy has yet to be established by long-term control studies. The incidence and severity of hepatotoxicity in daily therapy are in doubt and high-dosage intermittent therapy may be hazardous. In the present state of knowledge rifampicin cannot be recommended for routine initial therapy, and because of its high cost it is unsuited for use in economically undeveloped countries in currently used dosage. At present its principal value is to replace standard drugs where these are contraindicated because of intolerance or drug resistance.

Intermittent Chemotherapy

There is a great discrepancy between the best results attained by daily self-administered chemotherapy in controlled clinical trials and the results when the same regimen is used in routine practice. This discrepancy is almost entirely due to irregularity of self-medication.⁶³ Irregularity can be largely prevented by close monitoring of self-administered regimens by close interrogation of patients, home visits, tablet counting, and urine tests to confirm the patients are taking drugs. Alternatively, drugs may be given fully supervised. This becomes practicable where daily therapy is replaced by an intermittent regimen. Avoidance of irregular self-medication has been the principle spur to search for an effective twice-weekly regimen. Diminished toxicity and reduced cost are other possible advantages of intermittency. Streptomycin, 1 g, with isoniazid in the large dose of 15 mg/kg, administered supervised twice-weekly has been shown to be as effective as conventionally self-administered daily isoniazid and PAS.⁶⁴ Pyridoxine, 10 mg, is given with each dose to prevent isoniazid toxicity. Preliminary studies suggest that twice-weekly isoniazid 15 mg/kg with sodium PAS, 10 g twice-weekly, is another promising intermittent regimen.⁶⁵

Individual doses of drugs used in intermittent regimens usually need to be considerably greater than the daily dose. Some drugs—including streptomycin, sodium PAS, and ethionamide—cannot be increased above the conventional daily dose because of acute toxicity. The dose of other drugs—including isoniazid, pyrazinamide, and ethambutol—may be greatly increased with safety. Pyrazinamide and ethambutol, 90 mg/kg, may be given once weekly and isoniazid, 15 mg/kg, and ethambutol, 50 mg/kg twice-weekly, without toxicity.⁶⁶ The dangers of rifampicin, 1200 mg twice-weekly, have been mentioned above.

The efficacy of supervised intermittent drugs has been compared with self-administered drugs in two studies. In both studies continuation therapy with supervised twice-weekly streptomycin and isoniazid was compared with self-administered daily PAS and isoniazid, in one study,⁶⁷ and with self-administered thiacetazone and isoniazid in the other study.⁶⁸ No advantage for intermittency was shown in either study. Though the superiority of intermittent supervised regimens over daily self-administered regimens has not yet been established by comparative studies, undoubtedly it is the treatment of choice in selected patients who are known to be irregular with self-administered drugs.

Excellent results may be obtained either by carefully monitored self-administered therapy or by intermittent supervised therapy conducted by well-organized treatment services. Neither method can succeed where treatment services are poorly organized. The success of treatment in a community depends much more on the organization of the tuberculosis services than on the choice of chemotherapy regimen.

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Second Opinion, Please

Recurrent Urinary Infections in a Girl

ANDREW SMITH, HUGH JACKSON

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Rose Villa, Whickham, Newcastle upon Tyne

Dear Hugh,

A.B., aged 2, has just had her third urinary infection. The first presented as vomiting with slight fever and minimal diarrhoea and was diagnosed as gastroenteritis. When she began vomiting and was feverish a second time I microscopied her urine, found pus cells, and gave her sulphadimidine.

She got better slowly and a midstream urine specimen ten days later showed neither pus cells nor organisms. The third time she got the same symptoms I sent an M.S.U. to the lab. and

prescribed ampicillin. She responded quickly and was almost better when the laboratory report came back: *E. coli*—sensitive to everything except ampicillin!

Ought we to look for a congenital abnormality in her urinary tract?

Royal Victoria Infirmary, Newcastle upon Tyne

Dear Andy,

The information you gave me, plus the finding of 1,000 pus cells/mm³ in her urine, made it clear that A.B. had a urinary infection, so I admitted her with her mother for further investigation. Four M.S.U.s grew *E. coli* in significant numbers and also had significant numbers of pus cells, so the diagnosis was confirmed. Her I.V.P. was probably normal, though the demonstration was rather marred by overlying bowel shadows. Her urea was 50 mg%—a little raised—but electrolytes were normal.

In view of your culture results we discharged her on Septrin, 5 ml b.d., and will check her urine in six weeks.

Whickham, Newcastle upon Tyne and University of Newcastle upon Tyne

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